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Comments on Professor Hüseyin Özbey's letter

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Thank you very much for your comments related to our manuscript "Development of the human prepuce and its innervation" in the Supplement on Development of the External Genitalia in the journal Differentiation.

Being a pediatric urologist, it is evident that your comments come from the perspective of postnatal penile anatomy and surgical hypospadias repair. Accordingly, the issues that you raise fall outside of the perspective of our paper, which is fetal development of the human penis. Our failure to use the terms, "septum glandis" and "glans wings" is due to the fact that such postnatal anatomy is simply not present in fetal penile specimens (< 20 weeks of gestation).

It is sobering to realize that in some cases surgeons use anatomical terms that are not present in human anatomic texts. For example, your reference to "septum glandis" and "glans wings" are terms not found in human anatomic texts (Clemente, 1985; Moore, 1985; Rosse and Gaddum-Rosse, 1985; Warick and Williams, 1973). Another "surgical-based" departure from established human anatomy relates to your comment that "the glans penis doesn't cover the glanular urethra (fossa navicularis) circumferentially". Standard anatomical texts (Clemente, 1985; Moore, 1985; Rosse and Gaddum-Rosse, 1985; Warick and Williams, 1973) describe the "glans penis as the "anterior (expanded) end of the corpus spongiosum" with diagrams showing the urethra traversing through the glans and thus surrounded by spongiosal tissue. Our figure 7 of the human fetal glans clearly illustrates this point. Figure 2 in our paper, with which you have concerns, was redrawn accurately from Gray's Anatomy (Clemente, 1985) with one addition, not seen in Gray's Anatomy. We added the position of the frenulum in its correct position. We are intrigued by the MRI images of the postnatal human penis that you mentioned but respectfully consider histology the gold standard for fetal and early postnatal human penile anatomy. Moreover, the MRI images are surely of postnatal individuals and thus not relevant to human fetal penile development.

We agree that the hypospadiac penis has an anatomy different from than that of the normal penis (Baskin et al., 1998). Specifically, in hypospadias, glanular mesenchymal confluence does not take place, and the glans remains flattened. The main goal of surgical repair of hypospadias is to recreate a conical glans from a flattened glans by mobilizing a surgical plane between the abnormal glans and the corporal body. This results in the so called "glans wings" being brought to the midline to support the newly reconstructed urethra within the glans (Baskin and Ebbers, 2006). This technique has withstood the test of time with successful reconstructive outcomes (Baskin et al., 1994) (McNamara et al., 2015). We also agree that impaired or absence of normal glanular mesenchymal confluence results in absence of a "stand alone" glanular urethra and can lead to the rare but well-defined hypospadiac variant, megameatus intact prepuce (Baskin, 2017). In summary, we feel that our differences relate solely to surgical versus developmental perspectives on the topic.

We regret not including the elegant work of van der Putte which our data supports.

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